This prescribing information is intended for international use only and is based on the Summary of Product Characteristics (SmPC) for RECOMBINATE approved under MRP in certain member states of the European Union. Please always refer to the locally approved Prescribing Information before using the product.

RECOMBINATE

COMPOSITION
250 IU, 500 IU, or 1000 IU powder and 5 ml (50, 100 and 200 IU/ml of reconstituted solution) or 10 ml solvent for solution for injection (25, 50 and 100 IU/ml of reconstituted solution)
Active ingredient: Octocog alfa (human coagulation factor VIII produced by recombinant DNA technology in Chinese Hamster Ovary cells) 250 IU, 500 IU, or 1000 IU
Excipients: powder: human albumin, sodium chloride, histidine, macrogol 3350, calcium chloride dihydrate; for pH adjustment of powder reconstituted with 5 ml WFI: hydrochloric acid, sodium hydroxide.
 solvent: water for injections

INDICATIONS
Treatment and prophylaxis of bleeding in patients with Hemophilia A (congenital Factor VIII deficiency).
This product does not contain von Willebrand factor and is therefore not indicated in von Willebrand’s disease. RECOMBINATE is indicated for all age groups from neonates to adults.

POSOLOGY
The dosage and duration of the substitution therapy depends on the severity of the disorder of the hemostatic function, on the location and extent of bleeding episodes and on the clinical condition of the patient. The treatment should be carried out in collaboration with a physician with experience in bleeding disorders and a laboratory with the capacity to measure plasma AHF concentration.
The expected in vivo peak increase in RECOMBINATE level expressed as IU/dL of plasma or % of normal can be estimated by multiplying the dose administered per kg body weight IU/kg) by two.
Expected % Factor VIII increase = # units administered x 2% / IU / kg body weight (kg)
RECOMBINATE may also be administered for prophylaxis (short or long term) of bleeding, as determined by the physician on an individual basis.
For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days.
Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should
be performed to determine if a factor VIII inhibitor is present. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia. For more information on posology please refer to the full summary of product characteristics.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients. Known allergic reaction to bovine, mouse or hamster protein.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Severe allergic reactions to RECOMBINATE have been reported. Patients with known hypersensitivity to mouse, bovine or hamster proteins should be treated with caution. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. Facilities for the appropriate treatment of shock should be available.

If plasma AHF levels fail to reach expected levels or if bleeding is not controlled after adequate dosage, appropriate laboratory test to detect the presence of inhibitor should be performed.

The formation of neutralising antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with haemophilia A. The risk of developing inhibitors is correlated to the extent of exposure to Factor VIII, the risk being highest within the first 20 exposure days, and to other genetic and environmental factors. Rarely, inhibitors may develop after the first 100 exposure days. Cases of recurrence of inhibitors (low titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development.

RECOMBINATE contains 1.5 mmol sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

UNDESIRABLE EFFECTS
The following adverse reactions have been observed from spontaneous reporting and in clinical trials:

Common (≥1/100, <1/10): factor VIII inhibition\(^1\), chills.
Uncommon (≥1/1 000, <1/100): ear infection, dizziness, tremor, epistaxis, flushing, haematoma, hypotension, pallor, peripheral coldness, pharyngolaryngeal pain, nausea, hyperhydrosis, pruritus, rash, rash maculo-papular, pain in extremity, fatigue, pyrexia, acoustic stimulation tests abnormal.

Not known (cannot be estimated from the available data): anaphylactic shock, hypersensitivity, syncope, headache, cyanosis, tachycardia, dyspnea, cough, chest discomfort, wheezing, vomiting, abdominal pain, urticaria, skin exfoliation, loss of consciousness, paresthesia, angioedema, malaise, injection site reactions, chest pain.

\(^1\) In the PTP clinical trial (PTP = previously treated patients), none of the 71 subjects developed de novo FVIII antibody, but 22 of 72 evaluable per protocol PUPs (PUP = previously untreated patients) treated with Recombinate did develop FVIII antibodies and the above frequency was based on the PUP data. Of the 22, 10 were high titre (≥ 5 Bethesda Units) and 12 were low titre (< 5 Bethesda Units).

The formation of neutralizing antibodies, inhibitors, to Factor VIII is a known complication in the management of individuals with Hemophilia A. These inhibitors are invariably IgG immunoglobulins
directed against the Factor VIII procoagulant activity, which are expressed as Bethesda Units (B.U.) per ml of plasma.

The risk of developing inhibitors is correlated to the exposure to Antihemophilic Factor VIII, this risk being highest within the first 20 exposure days. The reported incidence of inhibitory antibodies in patients with severe hemophilia A who are at high risk for inhibitor development (i.e., previously untreated patients) is estimated in studies to be 31% for RECOMBINATE, which is within the reported range for plasma derived AHF. Patients treated with RECOMBINATE should be carefully monitored for the development of inhibitory antibodies by appropriate clinical observations and laboratory tests.

INCOMPATIBILITIES

RECOMBINATE must not be mixed with other medicinal products.

Only the provided infusion sets should be used because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

Medicinal product subject to medical prescription.

11/2014